Breast density, benign breast disease, and risk of breast cancer over time

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Abstract

Objectives

Assessing the combined effect of mammographic density and benign breast disease is of utmost importance to design personalized screening strategies.

Methods

We analyzed individual-level data from 294,943 women aged 50–69 years with at least one mammographic screening participation in any of four areas of the Spanish Breast Cancer Screening Program from 1995 to 2015, and followed up until 2017. We used partly conditional Cox models to assess the association between benign breast disease, breast density, and the risk of breast cancer.

Results

During a median follow-up of 8.0 years, 3697 (1.25%) women had a breast cancer diagnosis and 5941 (2.01%) had a benign breast disease. More than half of screened women had scattered fibroglandular density (55.0%). The risk of breast cancer independently increased with the presence of benign breast disease and with the increase in breast density (*p* for interaction = 0.84). Women with benign breast disease and extremely dense breasts had a threefold elevated risk of breast cancer compared with those with scattered fibroglandular density and without benign breast disease (hazard ratio [HR] = 3.07; 95%CI = 2.01–4.68). Heterogeneous density and benign breast disease was associated with nearly a 2.5 elevated risk (HR = 2.48; 95%CI = 1.66–3.70). Those with extremely dense breast without a benign breast disease had a 2.27 increased risk (95%CI = 2.07–2.49).

Conclusions

Women with benign breast disease had an elevated risk for over 15 years independently of their breast density category. Women with benign breast disease and dense breasts are at high risk for future breast cancer.

Key Points

- *Benign breast disease and breast density were independently associated with breast cancer.*
- *Women with benign breast disease had an elevated risk for up to 15 years independently of their mammographic density category.*

Keywords

Breast neoplasms
Mass screening
Longitudinal studies
Mammographic density
Benign breast disease

Abbreviations

BI-RADS	Breast Imaging Reporting and Data System
CI	Confidence interval
HR	Hazard ratio

Supplementary Information

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Introduction

High breast density and benign breast disease are major risk factors for breast cancer. Women with a high mammographic density are associated with a two- to fourfold elevated risk compared with women with fatty breast tissue [1, 2, 3, 4], while the presence of a benign breast disease doubles the risk of subsequent breast cancer [5]. Even though research has focused on each of these risk factors separately, little is known about the combined effect of these two factors, which has important implications to designing personalized strategies aimed at improving the effectiveness of breast cancer screening [6, 7].

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A prior study with limited sample size found a significant interaction between mammographic density and different subtypes of benign breast disease [8]. This finding is in contrast to a more recent large study that found no combined effect of mammographic density and different subtypes of benign breast disease with the risk of breast cancer [9]. The study population in the abovementioned studies was limited to women with benign breast disease only, and they assessed the effects of different benign breast disease subtypes, but they did not assess the presence or absence of a benign breast disease. Women with a benign breast disease and high mammographic density could be at very high risk for breast cancer and they may benefit from more intense follow-up strategies or different screening modalities.

Our aim was to evaluate the joint association between benign breast disease and mammographic density with the risk of breast cancer in the context of population-based breast cancer screening by using individual-level data from the long-standing mammography program in Spain.

Methods

Setting and study population

Mammographic screening in Spain follows the recommendations of the European Guidelines [10] and is publicly funded. The program started in 1990 in a single setting and became nationwide in 2006. Population-based screening in Spain has been previously described in detail elsewhere [11, 12, 13]. Briefly, the program is organized into administrative screening settings responsible for the local application of screening in their area. Women aged 50 to 69 years are invited every 2 years for a two-view mammogram (craniocaudal, and mediolateral oblique). All screening mammograms are interpreted by 2 trained breast radiologists and classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) scale or equivalent [12]. Prior mammograms are available for comparison at subsequent screens. Women with abnormal findings on mammographic interpretation are recalled for further assessments, including additional imaging, ultrasound, and invasive procedures. If no malignancy is detected, women are referred back to screening at 2 years, while women diagnosed with breast cancer are referred for treatment. All breast biopsies are histopathologically confirmed by trained pathologists.

Data for this study were obtained from four centers of the Breast Cancer Screening Program that routinely gather information on mammographic density (Costa de Ponent, Vallés Oriental, Sabadell-Cerdanyola, and Cantabria). Data for the study comprised information about women screened between 1996 and 2015, with follow-up until December 2017 for interval cancer cases. The centers collect information on screening mammography examinations, recall, further assessments, and diagnoses performed in their defined catchment areas. Approval for data analyses was granted by the review boards of the institutions providing data. Informed consent was not required since we used anonymized retrospective data.

Our study population consisted of 295,837 women aged 50–69 years with at least one BI-RADS breast density examination at screening mammography between January 1996 and December 2015. We excluded 894 women diagnosed with breast cancer at first screen as they did not have any follow-up. This left 294,943 women for the analysis.

Definition of study variables

The results of breast biopsies were classified by trained pathologists at each screening center. Women were considered to have a benign breast disease if, after exclusion of malignancy in a biopsy, the pathology report specified a diagnosis of benign breast disease. If women had more than one biopsy, we ensured that none of them confirmed malignancy in order to establish the presence of a benign breast disease. Lobular carcinoma in situ on biopsy was considered a benign breast disease.

Breast cancer cases included all invasive cancers and ductal carcinoma in situ regardless of whether they were screen-detected cancers, or interval breast cancers (those diagnosed within 24 months after a negative screening exam and before the next screening invitation). Breast cancer cases were identified from the screening center databases, population-based cancer registries, the regional Minimum Data Set, and hospital-based cancer registries.

Breast density was determined by breast radiologists at the time of screening as part of routine mammogram interpretation, using the BI-RADS density categories [14]: almost entirely fat (A), scattered fibroglandular density (B), heterogeneously dense (C), or extremely dense (D). If women had more than one mammographic density measure during the study period, we chose the breast density measured at the earliest screening examination. In case of discordance in breast density classification between radiologists, we chose the density classification assigned by the most expert radiologist. The BI-RADS B category was used as the reference group for mammographic density because it is the most common group and women with this category are considered to have an average risk of breast cancer.

Statistical analysis

Women were considered as the unit of analysis. For each woman, person-years at risk was calculated from the date of the first screen. For women with no history of benign breast disease, follow-up started at the date of the first screening participation and ended at the date of breast cancer diagnosis or 2 years after last mammography examination for follow-up of interval cancer cases, whichever came first. Women with a benign breast disease contributed person-years at risk to the "no benign breast disease group" from the date of the first screen until the date of diagnosis of first benign breast disease. They contributed person-years to the "benign breast disease group" from the date of diagnosis of the first benign breast disease. Similarly to women without a benign breast disease, follow-up for women with a benign breast disease ended at the date of breast cancer diagnosis or 2 years after last mammography examination for follow-up of interval cancer cases, whichever came first.

We compared the frequency distributions of various risk factors for women with and without breast cancer: presence or absence of a benign breast disease, BI-RADS density category at the earliest examination, and age at the first screen (in 5-year age groups). In addition, rates of breast cancer by the presence or absence of a previous benign breast disease and BI-RADS density category were calculated as the number of breast cancer cases divided by the number of women-years at risk in each group. Confidence intervals for rates were calculated using exact Poisson distribution.

We used a partly conditional Cox proportional hazards model to estimate the hazard ratios and 95% confidence intervals of the association between benign breast disease and mammographic density with the risk of breast cancer [15]. By using a partly conditional Cox model, we included all screening mammograms in each individual, incorporating benign breast diseases occurring after the first screening participation and accounting for within-woman correlation. We tested whether there was an interaction between previous benign breast disease and breast density with the risk of breast cancer.

To control for possible confounders such as changes in BI-RADS classification or technical changes over time, all models were adjusted for age at screen (continuous) and year of screen (continuous). The proportional hazards assumption was ascertained by plotting the log-minus-log of the survivor function against log time for each predictor variable. The tests found no evidence of violation of the proportional hazards assumption between the covariates and time.

We performed three sensitivity analyses. First, we limited the outcome to invasive breast cancer only. Women with DCIS were censored at the time of diagnosis and they were not included as breast cancer cases. Second, to test the effect of repeated breast density measures in the same person over the study period, we performed the analyses using the latest mammographic density measure for each woman instead of the earliest. Third, to test if women at higher risk had a higher proportion of interval cancer cases than those at lower risk, we performed an analysis of interval breast cancers as outcome. Women with screen-detected cancer were censored at the time of diagnosis and not included as breast cancer cases. All tests were two-sided with a 5% significance level. Statistical analyses were conducted in R 3.4.2 (R Foundation for Statistical Computing).

Results

Women in the study population had a median follow-up of 8.0 years. Out of the 294,943 women in the study population, 3697 (1.25%) had a diagnosis of breast cancer and 5941 (2.01%) had benign breast disease. The proportion of previous benign breast disease was higher among women with breast cancer than in those without breast cancer (2.6% and 2.0%, respectively) (Table 1). At baseline examination, BI-RADS scattered fibroglandular density (B) was the most common category for women with and without breast cancer (49.5 and 55.1%, respectively). Among women with breast cancer, there was a higher proportion of women with high mammographic density (BI-RADS density categories C or D), and a larger proportion of women aged 55 to 64 years.

Table 1

Baseline characteristics of women in the study population

	No breast cancer, *N* = 291,246	**Breast cancer, *N* = 3697**	***p***
Benign breast disease			
No	285 400 (98.0%)	3 602 (97.4%)	*
Yes	5 846 (2.0%)	95 (2.6%)	*
Breast density			
Almost entirely fat	60 343 (20.7%)	498 (13.5%)	*
Scattered fibroglandular	160 496 (55.1%)	1 831 (49.5%)	*
Heterogeneously dense	44 386 (15.2%)	724 (19.6%)	*
Extremely dense	26 021 (8.9%)	644 (17.4%)	*
Age at first screen			
50–54	187 829 (64.5%)	2 181 (59.0%)	*
55–59	56 149 (19.3%)	915 (24.7%)	*

*Different at $p < 0.05$ in a two-sided test of equality for column proportions (*z*-test). Tests are adjusted using the Bonferroni correction for multiple comparison. Using the Breast Imaging Reporting and Data System (BI-RADS) density categories: A = almost entirely fat; B = scattered fibroglandular densities; C = heterogeneously dense; D = extremely dense

	No breast cancer, $N = 291{,}246$	Breast cancer, $N = 3697$	p
60–64	35 455 (12.2%)	543 (14.7%)	*
65–69	11 813 (4.1%)	58 (1.6%)	*

*Different at $p < 0.05$ in a two-sided test of equality for column proportions (z-test). Tests are adjusted using the Bonferroni correction for multiple comparison. Using the Breast Imaging Reporting and Data System (BI-RADS) density categories: A = almost entirely fat; B = scattered fibroglandular densities; C = heterogeneously dense; D = extremely dense

The distribution of mammographic density categories by the presence or absence of benign breast disease is shown in Table 2. The most frequent mammographic density category was scattered fibroglandular for women with and without benign breast disease (50.6% and 55.1%, respectively). Compared with those without benign breast disease, women with benign breast disease had a higher proportion of extremely dense breasts (15.6% and 8.9%, in women with and without a benign breast disease, respectively), and a lower proportion of entirely fatty breasts (12.4% and 20.8%, respectively).

Table 2

Frequency and prevalence of breast density categories by presence or absence of a benign breast disease

	Bi-RADS breast density				
Benign breast disease	**Almost entirely fat**	**Scattered fibroglandular**	**Heterogeneous**	**Extremely dense**	**Total**
No BBD	60 106 (20.8%)	159 318 (55.1%)	43 842 (15.2%)	25.736 (8.9%)	289 002
BBD	735 (12.4%)	3 009 (50.6%)	1 268 (21.3%)	929 (15.6%)	5 941

BBD benign breast disease

Table 3 shows the overall rates of breast cancer by the presence or absence of benign breast disease and by BI-RADS density categories. Among women with scattered fibroglandular breasts, the rate of breast cancer per 1000 women-years at risk was 2.43 (95%CI 1.68–3.17) and 1.46 (95%CI 1.40–1.53) for those with and without benign breast disease, respectively. For women with extremely dense breasts, the rates per 1000 women-years were 3.95 (95%CI 2.30–5.60) and 2.97 (95%CI 2.74–3.21) for those with and without benign breast disease, respectively.

Table 3

Overall rates of breast cancer by presence or absence of a benign breast disease

	Women-years at risk	Number of cases	Breast cancer rate (95%CI) per 1000 women-years (‰)
No benign breast disease			

	Women-years at risk	Number of cases	Breast cancer rate (95%CI) per 1000 women-years (‰)
Almost entirely fat	488,452	490	1.00 (0.91–1.09)
Scattered fibroglandular	1,222,576	1790	1.46 (1.40–1.53)
Heterogeneous	314,808	700	2.22 (2.06–2.39)
Extremely dense	209,134	622	2.97 (2.74–3.21)
Benign breast disease			
Almost entirely fat	4188	8	1.91 (0.59–3.23)
Scattered fibroglandular	16,901	41	2.43 (1.68–3.17)
Heterogeneous	7076	24	3.39 (2.03–4.75)
Extremely dense	5556	22	3.95 (2.30–5.60)

The ~~HR~~risks associated with each combination of mammographic density and benign breast disease are shown in Table 4. No significant interaction was found between previous benign breast disease and mammographic density (p for interaction = 0.84). The risk of breast cancer increased with increasing mammographic density and with the presence of benign breast disease. Compared with women with average breast density (scattered fibroglandular) and no benign breast disease, women with low breast density and no benign breast disease had a lower risk of future breast cancer (HR = 0.65; 95%CI = 0.59 to 0.72). In contrast, the risk for those with low breast density and a benign breast disease was similar to the average reference group (HR = 1.29; 95%CI = 0.64–2.58). Women with heterogeneous mammographic density had an elevated risk of breast cancer, both those with and without benign breast disease (HR = 2.48, 95%CI = 1.66–3.70; and HR = 1.58, 95%CI = 1.44–1.72, respectively). Similarly, women with extremely dense breasts were at the highest risk of future breast cancer, independently of whether they had benign breast disease or not (HR = 3.07; 95%CI = 2.01–4.68; and HR = 2.27, 95%CI = 2.07–2.49, for women with and without benign breast disease, respectively).

Table 4

Breast cancer risk by breast density and benign breast disease

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	BI-RADS breast density, HR (95%CI)			
Benign breast disease	**Almost entirely fat**	**Scattered fibroglandular**	**Heterogeneous**	**Extremely dense**
Hazard ratios relative to women with no benign breast disease and scattered fibroglandular density. Adjusted for age at first screen, and year of screen				
p value for interaction between benign breast disease and breast density = 0.84				

BI-RADS breast density, HR (95%CI)				
Benign breast disease	**Almost entirely fat**	**Scattered fibroglandular**	**Heterogeneous**	**Extremely dense**
No BBD	0.65 (0.59–0.72)	ref.	1.58 (1.44–1.72)	2.27 (2.07–2.49)
BBD	1.29 (0.64–2.58)	1.68 (1.24–2.29)	2.48 (1.66–3.70)	3.07 (2.01–4.68)
Hazard ratios relative to women with no benign breast disease and scattered fibroglandular density. Adjusted for age at first screen, and year of screen				
p value for interaction between benign breast disease and breast density = 0.84				

We examined the cumulative incidence curves of breast cancer for benign breast disease within breast density strata (Fig. 1). The figure depicts how the occurrence of breast cancer cases follows a staggered 2-year pattern given by the biennial screening participations of women in the programs. The risk of developing breast cancer diverged over time among women with and without benign breast disease, independently of the BI-RADS density strata. The probability of developing breast cancer 15 years after the index mammography examination for women without benign breast disease increased as mammographic density increased, ranging from 1.5% (95%CI = 1.3–1.7) for women with almost entirely fatty breasts to 4.8% (95%CI = 4.2–5.4) for those with extremely dense breasts. For women with a benign breast disease, the probability of breast cancer 15 years after the index mammography ranged from 3.4% (95%CI = 1.1–5.7) for those with almost entirely fat breast to 7.0 (95%CI = 4.1–9.9) for extremely dense breast.

Fig. 1

Adjusted survival curves for each mammographic density strata based on Cox proportional hazards model for women with and without benign breast disease. Models are adjusted for age at the first screen and the year of screening. The solid line represents women without benign breast disease; the dashed line represents women with a benign breast disease diagnosis

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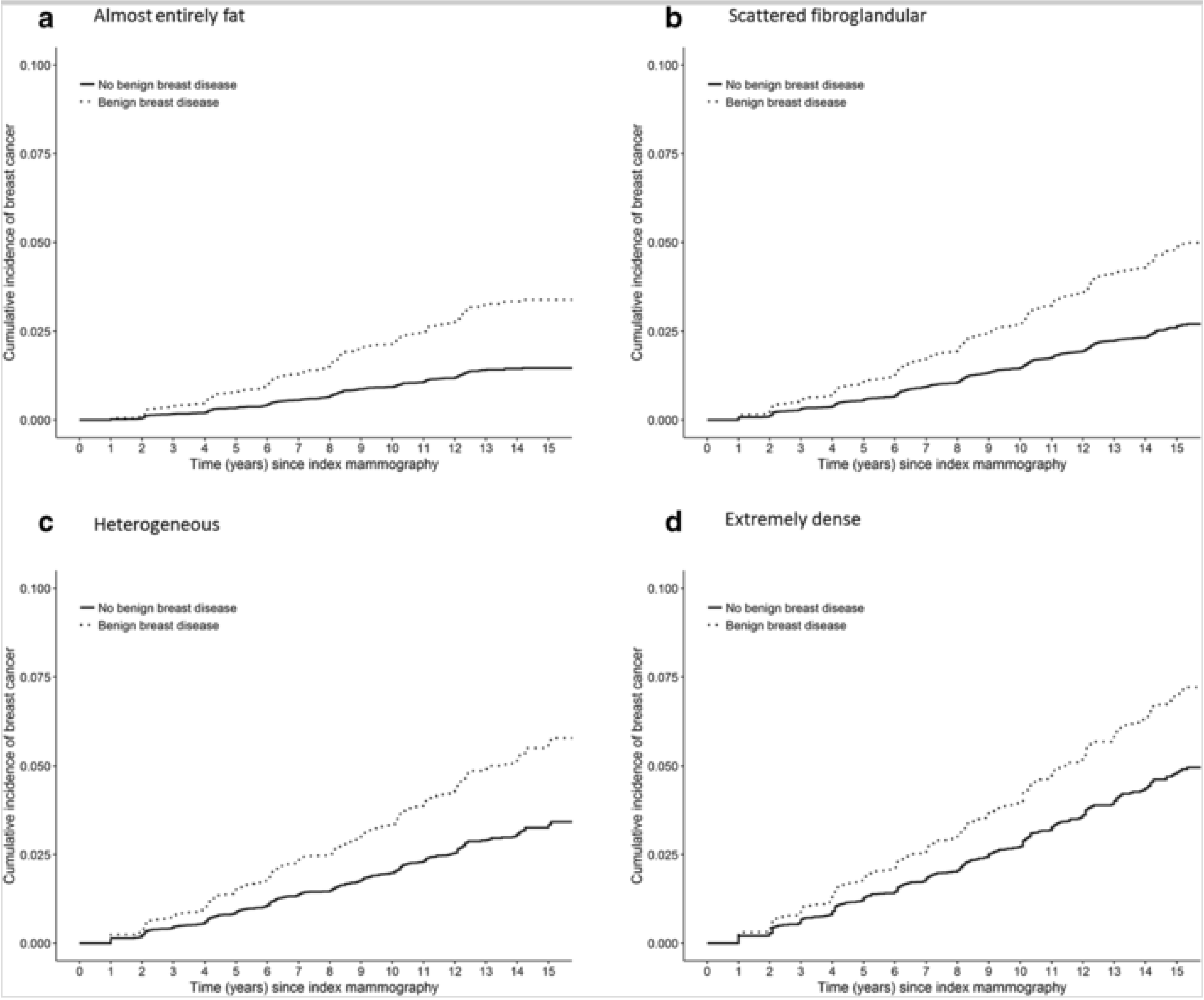

Sensitivity analyses excluding DCIS and including invasive breast cancer only as outcome were consistent with the full model and produced very similar estimates (Supplementary material, Table 1). In addition, the effect of choosing the latest rather than the earliest mammographic density measure had limited impact on the risk estimates (Supplementary material, Table 2). Lastly, the analyses of interval breast cancers as outcome had a ~~limited~~small number of cases, which limited the statistical power. However, the analyses showed that the risk for interval breast cancer was higher in women with benign breast disease, and the risk increased as breast density increased (Supplementary material, Tables ~~4~~3 and 4~~5~~).

Discussion

In this analysis of data from more than 290,000 women with a follow-up of more than 15 years, we examined the combined contribution of benign breast disease and mammographic density to the risk of breast cancer. We found that the presence of benign breast disease and high mammographic density were independently associated with an increase in the risk of breast cancer. The risk diverged over the study period for women with and without benign breast disease across mammographic density categories. The highest risk for breast cancer was found in women with benign breast disease and extremely dense breasts. Few studies have evaluated the combined effect of benign breast disease and breast density on the risk of breast cancer at mammographic screening. We used long-term population-based data from women participating in breast cancer screening to assess how benign breast disease and breast density affect the risk of breast cancer.

Consistent with most studies, we found that mammographic density was associated with breast cancer risk [16, 17, 18]. We observed that higher BI-RADS breast density categories were associated with an increased risk of breast cancer. In addition, there is consistent evidence that women with a benign breast disease are at an increased risk of breast cancer [5, 19]. A prior large study assessed the combined effect of mammographic breast density and different subtypes of benign breast disease, in a population of women with the presence of benign breast disease [9]. That study also found that mammographic density and benign breast disease were independent risk factors for breast cancer. However, the study population in the abovementioned study consisted solely of women with a benign breast disease, limiting their ability to compare the effect of the presence or absence of a benign breast disease. Despite these differences in study population and referent group, the results of the two studies are consistent.

Previous benign breast disease and mammographic density are risk factors commonly included in most individualized risk prediction models for breast cancer, including the Breast Cancer Surveillance Consortium, and Tyrer-Cuzick models [20, 21]. The finding that both factors are independent risk factors for breast cancer consolidates their utility in risk prediction models. However, although risk prediction models for breast cancer have a high expected to observed ratio, their discrimination accuracy is moderate, with potential for improvement [22]. Women with benign breast disease diagnosed at mammography represent 2.0% of the study population of women screened. Among those, half of them had dense breast (heterogeneous or extremely dense). Although uncommon (1%), these women could benefit from more intense screened strategies or different screening techniques as ultrasound or MRI. On the other hand, 20% of the study population had almost entirely fat breast density and absence of a benign breast disease. These women could be candidates for de-intensified screening strategies with longer screening intervals (3 or 4 years). Results from randomized controlled trials like MyPeBS or Wisdom studies will provide evidence on the effectiveness of personalized strategies [23, 24].

We excluded from the analyses women with a screen-detected cancer diagnosed at prevalent screen. This was done because these women did not have any disease-free follow-up, and they could not contribute time at risk to the estimates. Because high breast density is associated with younger age, and there is a known masking effect of breast density, excluding prevalent cancers detected at mammography could entail that some cancers might have been missed in women with dense breast that would later come out as incident cancers. Thus, our associations may slightly overestimate the true strength of the associations between denser breast and the risk of subsequent breast cancer.

This study has several potential limitations. Breast density was reported by radiologists as part of routine screening practice, and their results are likely to be less precise than they would have been if an automated density measure had been used. The inter-rater agreement of the BI-RADS breast density classification is moderate in most studies [25, 26], even in our study population [27]. Despite the moderate inter-rater agreement, our results are consistent with those published by other studies using BI-RADS breast density [4, 28, 29]. Breast density was classified by highly trained radiologists with more than 1000 screening mammograms read per year. Another limitation of the study is that criteria for density classification in the BI-RADS Atlas have changed over time and women who might previously have been classified as BI-RADS density category B are now defined as BI-RADS C if there is any dense area that could mask a tumor [30]. Nevertheless, the BI-RADS classification has been shown to appropriately discriminate women at different risks for breast cancer, with a fourfold gradient in risk between BI-RADS categories A and D [31]. Also, there was a transition from film mammography to digital mammography during the study period. Screen-film mammography was the default technique at start-up. Full-field digital mammography was introduced in 2004 and gradually became widespread. In 2015, 59% of mammography examinations were performed with full-field digital mammography. The transition from film to digital mammography might have had an effect on mammographic density classification and the detection rate, although previous studies have shown that these outcomes were not affected by the introduction of digital mammography [32, 33]. To offset the effect of changes in BI-RADS density classification and the transition from screen-film to digital mammography, our analyses were adjusted by year of screen, but the effect of the adjustment on the risk estimates was minimal. Another limitation was that the number of breast cancer cases after diagnosis of a benign breast disease was small, particularly those associated with fatty breast and extremely dense breast, which limited our ability to perform analyses by subtype of benign breast disease, or other sub-group analyses. Analyses by subtype of benign breast disease would have been desirable as previous studies have shown that breast cancer risk varies by subtype [5, 9, 19]. Lastly, individual information on risk factors such as body mass index, hormone therapy use, and menopausal status were lacking because the screening centers did not collect these information. These factors are known to be associated with mammographic density and with breast cancer risk. Adjusting for these and other confounding factors would have been desirable and could have refined our estimates.

A major strength of this study is that the data were obtained from a well-established population-based screening program with an average participation rate of 67% of invited women, and a re-attendance rate of 91.2% [12]. We analyzed information obtained from over 15 years of follow-up, which guaranteed sufficient time to provide robust estimates. This is the first large longitudinal study to examine the effect of previous benign breast disease and mammographic density in population-based mammography screening.

Conclusion

In summary, we found that benign breast disease and high mammographic density independently predicted the risk of breast cancer. The risk of breast cancer was lowest in women whose breasts were almost entirely fat and highest in women with benign breast disease and extremely dense breasts. The risk remained elevated over 15 years. This information could be used when discussing the potential benefits and harms of personalized screening strategies.

Publisher's note

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Methodology • retrospective

• ~~r~~observational

• ~~r~~multicenter study

Supplementary Information

ESM 1

(DOCX 84 kb)

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